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Development of an AI-Based Optimization System for Tandem Mass Spectrometry

Carla M. Wong
Hal R. Brand

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DEVELOPMENT OF AN AI-BASED OPTIMIZATION SYSTEM FOR TANDEM MASS SPECTROMETRY

Carla M. Wong and Hal R. Brand

Lawrence Livermore National Laboratory
Chemistry & Materials Science Department
P. O. Box 808, L-365
Livermore, CA 94550

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Lawrence Livermore National Laboratory

P.O. Box 808, Mail Stop L-365, Livermore, CA. 94550

ABSTRACT

Triple quadrupole mass spectrometers (TQMS) are very complex, computer-controlled, multiparametric instruments which require optimization or selective tuning of over 30 operational parameters in five different operational modes. They generate incredible amounts of multidimensional data and require considerable expertise for both operating the instrument and interpreting the data. Much of this expertise is the kind of knowledge that can be represented as procedures, or rules, of the type described in artificial intelligence (AI) research. In the expert-system, knowledge-base environment it is possible to encode a tuning procedure, including heuristics, to create a system that is capable of optimization of the data acquisition process throughout the entire mass range of the TQMS. Now, the tuning of a mass spectrometer no longer has to be limited to the traditional "average tuning" where the sensitivity in both the high and the low mass ranges is compromised to achieve the instrument "tuned state". Instead we can

optimize the peak intensity throughout the entire mass range. Another advantage to this approach is that we will have the ability to control the instrument so that only the data most relevant to the experiment will be collected. This ability to heuristically control instrument operational and data acquisition parameters while actually running an experiment will have a number of advantages; the most important of which is the ability to redefine the data you want to collect next. This means that experiments become information driven rather than just data driven. The TQMSTUNE knowledge-based expert system enables us to optimize the instrument operational parameters based on rules associated with peak shape, intensity, resolution, interactions between tuning parameters and compound and mass differences. The expert system rules actually extend the normal method of tuning the TQMS in MS/MS operational mode, simply because it is too time consuming to achieve this level of optimization manually. An expert system can do optimized tuning while unattended and create files of optimized parameters ready to access in real time as a sample is being analyzed.

1. INTRODUCTION

Artificial intelligence (AI) is that branch of computer science which attempts to understand and model intelligent behavior with the aid of computers. In general these attempts to have machines emulate intelligent behavior fall far short of the competence of humans.

However, in the area of expert systems, computer programs have been developed which can achieve human performance, and in limited aspects, even exceed it.

These programs, or expert systems, use a knowledge base of facts, heuristics (rules-of-thumb) and other information about a problem, joined with rules about how to apply this knowledge and how to make inferences using it. These programs differ from conventional computer programs in that they are not algorithmic and they often make conclusions based on incomplete or uncertain information. In general the power of an expert system is proportional to the size of the knowledge base (i.e. the amount of information in the knowledge base, not the number of rules which is only the method of reasoning about the knowledge).

In order to build an expert system, the problem domain must be well-bounded, there must be at least one human expert who is known to perform the task well, and the expert must be able to explain the methods used to apply the knowledge to a task.

We will describe the evolution of the AI guided optimization programs at our laboratory, starting with a simple prototype system and progressing to the more powerful, effective and functionally useful system currently implemented at our laboratory. Examples of how this system has been applied to real problems are provided.

2. PROBLEM STATEMENT

Triple quadrupole mass spectrometers (TQMS) consisting of an ion source, quadrupole mass analyzer, an rf-only quadrupole collision gas chamber, a second quadrupole mass analyzer, and an ion detector have been described previously.[1-4] The most common use of these multistage instruments is for mixture analysis using the normal mass spectra and daughter spectra operating modes. The many ionic species formed in the source are separated in the first quadrupole mass analyzer by mass-to-charge ratio (m/z), further fragmented by low-energy collisionally activated dissociation (CAD) in the rf-only quadrupole collision gas chamber where all masses are passed, and the resulting fragment ions are then mass analyzed by the second quadrupole mass filter. This entire system provides enhanced selectivity and sensitivity over conventional mass spectrometers. The daughter spectra mode plus four other modes of operation are illustrated in Fig. 1, which amply illustrates the many types of data available from these systems, when each operational mode has fixed operational parameters. It has been shown that these operational modes need not have fixed instrumentation parameters. In fact, information <u>enhancement</u> can be achieved by varying instrumental operational conditions for each data acquisition mode and since there are five modes, there is a need for computer aided optimization. Also, because of flexible and rapid changes in operational modes, a tremendous amount of data is generated.[5-8] The problem then becomes one of optimizing data acquisition to get the best possible answer rather than just the most possible data. The ultimate goal of this project is to have the computer run the experiment and determine which data should be acquired to fulfill the researcher's goals and determine how the instrument operational conditions should be optimized to acquire that data. This is particularly important in kinetics studies of transient species, such as those found in high explosives and oil shale pyrolysis studies.

The multidimensional nature of the mass spectrometric data produced is shown in Figure 2, a spectra of sulfur compounds in a complex pyrolysis gas mixture. The baseline or x-axis represents the amu or atomic mass unit of the various ions in a normal mass spectrum. The vertical or y-axis is the relative intensity or amount of each ion present in the sample. The split at the top of each peak illustrates the key ions that would be produced in <u>daughter mode</u> if that particular peak or ion was selected and refragmented. For example, at mass 84, daughter or fragment ions produced at masses 53 and 45 would indicate thiophene. The process illustrates the inherent selectivity and specificity in TQMS data.

The purpose of this research is to simulate or reproduce the intelligent behavior of a human expert in optimizing the triple quadrupole mass spectrometer (TQMS). The system will not learn in the true sense of the word "learn", but it will grow in knowledge as more information is transferred from the human expert to the system. Another advantage of the system is that it will not be prone to forgetfulness, time constraints, daydreaming or boredom. It will eventually do better than the human expert on a day-to-day basis simply because humans do not have the time, patience and willingness to tune mass spectrometers by optimizing the spectra over the entire mass range; instead, they tune by just normalizing the spectra throughout the mass range.

3. PROPOSED METHOD OF SOLUTION

To reproduce the intelligent behavior of the human TQMS experts, we have implemented a computer model of the procedures used by the human expert to accomplish the tuning task. This model serves as the framework for the implementation of the AI expert system. The general model of tuning could be viewed as a problem in conventional control theory with the operator as the controller, that is:

1. The operator decides on parameters and sends them to the instrument.
2. The instrument runs for a short time taking measurements and sends them to the operator.
3. The combination of operator input parameters and instrument output measurements comprises the tuning procedure.

However, upon close analysis, the conventional control system approach doesn't work because it relies on being able to model precisely the physical processes of the instrument, which isn't possible. In the expert systems approach, the goal is to codify the human operator's knowledge or experience and how he/she uses this knowledge in the tuning. There is no attempt to analyze this experience or to arrive at a theory to explain it.

Therefore, from an expert system point of view, instrument tuning can be conducted within the context of a three level hierarchy of operator activities.

A. Lowest level - operator analyzes results of tuning and makes some interpretation as to the state of the instrument - i.e. dirty source - voltage too low or too high on SEM, gas pressure too low or too high in CAD region, etc.

B. Second level - operator selects, executes and monitors a plan depending on the interpretation of A.

C. Highest level - plans are grouped into strategies and the operator selects the best strategy for tuning a particular operational mode.

Using this concept of operator activity, our current model of the behavior of the human expert is correlated with:

(1) The operator's knowledge of the actual TQMS instrument to determine which knob, when "tweaked" (turned to optimize on a single parameter) will improve tuning the most;

(2) The actual turning of the knobs; a process which is different for some knobs or knob sets; and,

(3) The operator's goals and knowledge of knob interactions, which may be different each time a knob is tweaked. For example, if the expert has been having problems with the peak resolution, then the goal may be to chose a final knob value that produces only a small increase in peak height as opposed to a value that

greatly increases the peak height but also moves the peak width outside the range of proper resolution; or, if after tweaking a given knob, the value changes significantly with respect to other knobs known to have interactions, a repeat tweaking of correlated knobs will be done.

The knowledge involved in these operator activities is composed (in varying parts) of:

1. Physical knowledge of the TQMS, i.e. what knobs effect what assemblies, and the relative and absolute position of those assemblies.
2. A priori knowledge of the operational principles of the TQMS, i.e. the physics of lenses and quadrupoles.
3. Heuristic knowledge of the effects and interactions of the knobs.
4. Recent historical knowledge of which knobs have already been tweaked, and how much was gained in tweaking those knobs.
5. Heuristic knowledge of how much signal can be expected from the tuning gas and its pressure in the source.
6. Heuristic (and a priori) knowledge about how the tune state changes as a particular knob is tweaked.
7. Experiential knowledge about the most likely value (or range) that a given knob(s) should have when the TQMS is optimally tuned.

The kind of information needed by the expert system for tuning a mass spectrometer can thus be described in terms of what the "human" expert actually does. At present, this person watches peaks on an oscilliscope while turning knobs on the TQMS controllers. What the expert is tuning for while watching the oscilliscope is not a single effect such as increased intensity, but a complex interaction of several effects we term "goodness". The "human" expert must describe in precise terms what makes a peak "good". These terms involve height and standard deviation of height, the standard deviation of the fit of a line to the peak, the width at the 10%, 50% and 90% peak height, the ratios of intensities for various masses, resolution, sensitivity, reproducibility and a smooth, symmetrical peak shape.

4. EVOLUTION OF TQMSTUNE

The TQMSTUNE Expert System was initially designed to relieve the TQMS experts from the burden of daily tuning. Within a short time, the system's design was expanded to encompass multiple mass range and single peak tuning to greatly increase sensitivity. During TQMSTUNE's three year lifetime, it has moved through three versions. Significant performance improvements have been realized with each version.

4.1 TQMSTUNE Version 1.

The initial implementation of TQMSTUNE was designed to mimic the full mass range tuning as normally done by the TQMS experts. As such, the system compromised the intensity of most individual mass peaks over the full mass range to achieve the best overall tuning.

To achieve the tuning throughout the mass range as represented by the "good tuning" vs. "bad tuning" example in Figure 3 normally takes 1/2 hour for an expert. In these first attempts shown in the illustrative photos taken from the oscilloscope in Figure 4, only the peak intensities were maximized. There were no peak shape or resolution factors taken into account. In comparing the expert human manual tuning with the AI tuning, the intensity is better than manual tuning but the peak shape and resolution were far worse as indicated by the noise spikes on top of the peaks and the lack of resolution between adjacent peaks. These first attempts used an AI or expert system program which invoked an "Interpret-Instructions method" called CALIBRATE. That "method" then coarse tuned the instrument in 6 minutes throughout the mass range.

4.2 TQMSTUNE Version 2.

The next step in the evolution of the AI tuning program combined intensity, peak-shape and resolution into a single figure of "goodness" for each reading. This "Goodness" function was used for optimum tuning on a single mass rather than looking at the entire mass range. A separate file of optimum tuning parameters was created in 11 minutes for each mass and the multiple tuning files which were developed by the AI program could be used by the instrument computer to optimize 20 mass dependent parameters, on-the-fly, in 7.7 msec.

The top two photos from the oscilloscope in Figure 5 show the results of this "Goodness" factor incorporated into the program. The AI tuning resolution was as good (or better) throughout the entire mass range as the manual tuning and the peak shape was somewhat better; but, the sensitivity was slightly worse. The bottom two photos show the shape of the top of the mass 69 peak. The AI tuning was slightly better, (i.e., no splitting at the very top of the peak) but the intensity is slightly lower.

The reasoning in this version of "TQMSTUNE," was rule-based with production rules of the form: "If PREMISES then CONCLUSION." These rules were controlled by "backward chaining", a search strategy which views a conclusion as an initial hypothesis which is assumed to be true. The initial hypothesis is stated explicitly in the knowledge base. The rule interpreter tests the evidence for truth of the hypothesis and if the premises are true then the interpreter concludes the hypothesis is true.

An example of the rule structure used is illustrated in Figure 6. Three rules are shown here. The first one, a rule for tuning the field axis (FA) says that if the tune "goodness" (i.e. all aspects of height, shape and resolution for each peak) is maximized on each of the quadrupole sections (Q1, Q2 and Q3) then the "tune-goodness" is maximized from tuning these particular parameters, (i.e. field axis).

Instrument tuning was performed in two stages: coarse tuning, which involved changing voltages by large amounts over the entire useful range for each parameter followed by fine tuning, which repeated the procedure using small increments over a narrow range. Proper sequencing was controlled by judiciously linking the rules through their premises and conclusions so that the backward chaining control structure would examine the rules in the desired order. Actual tuning of the instrument occurred as the backward chainer examined the appropriate rule premises. Each of these premises invoked a "method" to vary a particular instrument parameter.

In addition to the rules for instrument tuning, Version 2 of TQMSTUNE also used a set of sequential instructions having a form nearly identical to rule premises to set up initial conditions and otherwise prepare the TQMS for tuning. These instructions were invoked by a "method" just before the backward chainer was invoked on the tuning rules.

To use that system "TQMSTUNE" was loaded and a schematic drawing of the TQMS was displayed. The drawing consisted of icons for the mass spectrometer source, lenses, rod assemblies and detector as shown in Figure 7. Gauges could be attached to each unit of the TQMS to monitor the voltage as it was being changed by the invoked "method" of the rule system. Using the mouse and pointing at "INITIALIZE" and then "TUNE" from the "CHEZ TQMS" <u>menu</u> started the tuning process. The component voltages were set to initial values obtained from the RT-11 control computer calibration file, the sequential instructions were invoked, and finally, the tuning rules were invoked. TQMSTUNE sends instructions to each device to vary control parameters while checking each device for coarse, then fine tuning. Following requests from TQMSTUNE, RT-11 acquired data and passed those measured and derived parameters to TQMSTUNE. TQMSTUNE then plotted the progress of the tuning procedure for each device in a separate window as a function of overall "GOODNESS" or "INTENSITY" vs. voltage.

A more detailed look at maximization of "tune GOODNESS" vs. voltage for each parameter is shown in Figure 8. A specific example is shown and a vertical "tic mark" on the plot shows which specific point was chosen by the program as the best point for optimization with respect to the particular parameter, Q1 Field Axis.

4.3 TQMSTUNE Version 3.

In order to increase the versatility of TQMSTUNE so as to handle MS/MS tuning, and to more properly reflect the thought patterns of the experts, the system underwent a major metamorphosis. The current version of TQMSTUNE now tunes the TQMS using three iterative steps:

1. Select the knob (or instrument parameter) to vary that will "most improve" the tune state. If no knob can be selected, then the tuning is complete.
2. Select the way in which the optimization of the knob will be done, the type of data optimized (e.g. Goodness or Intensity), and the limits within which the optimization will take place.

3. Use the selected robust (noise-tolerant) optimization algorithm to optimize the selected data by varying the selected knob.

This design uses a "method" to encode the sequencing of the iterative steps, rules to handle the complex, heuristic decisions in the first two steps, and "methods" to implement the optimization algorithms.

A number of significant advances were made by this metamorphosis. First, the system now expressly selects instrumental parameters (knobs) for optimization, rather than having the optimization occur as a side effect of examining the premise of a rule. Second, the system now makes much better use of feedback as instrument performance is evaluated before a knob is selected for optimization. In this way, the current system is much more adaptable to various tuning problems with its adaptability being limited only by its rules. Finally, the system is now more flexible as it allows knobs to be optimized by any number of expressly selected optimization schemes.

5. KNOWLEDGE REPRESENTATION IN THE TQMS DOMAIN

The hybrid knowledge representation environment of Frames, Methods, Rules, and Active Values provided by KEE (Knowledge Engineering Environment, an expert system shell from Intellicorp, Inc. of Mountain View, CA) permits significant flexibility in the representation of knowledge about the instrument, its tuning procedure, and interfacing. Frames are a way to provide a very clear and simple representation of the declarative knowledge about the instrument parts and controls.

Methods are valuable for representing procedural knowledge about the time sequencing of the steps in tuning the TQMS, and for implementing the standard algorithms necessary to interface the expert system to the LSI-11 computer used to control the TQMS. A flexible interface between Methods and the rule interpreters allows the knowledge of the iterative steps in tuning the TQMS to be simply and clearly represented in a Method, while concurrently permitting the use of rule sets for the complex decision steps required during each iteration in the tuning process.

Rules, using the backward chaining rule interpreter, are used to represent the knowledge to make the decision of which knob to adjust (or "tweak") at each step in the tuning process. This largely heuristic and poorly defined knowledge was easy to represent in Rules for two reasons. First, Rules provided a procedural knowledge representation scheme that was readily understood by the experts, which facilitated information transfer from the experts to the expert system. Second, using Rules provided for easy incremental addition/modification to the knowledge about knob selection because new Rules could be added without regard to their placement or order of use. Rules allowed the experts to concentrate on expressing knowledge about knob selection and not on the decision control structure.

Another feature of KEE which facilitated a natural representation for the value of an instrument control parameter, or knob was "Active Values". Active Values provided a mechanism that associates the procedural knowledge about interfacing to the LSI-11 computer controlling the TQMS with the "Setting" slot of each knob frame. By attaching an active value on the "Setting" slot of each knob frame, Methods are invoked at each access to the "Setting" slot. These Methods cause the instrument's physical knob settings to track the "Setting" slot in the knob frames. The advantage of this interfacing scheme is the invisibility of the instrument interface to the rest of the system. An additional advantage is a simulated instrument can be attached to the expert system in exactly the same way, thereby permitting development and testing of the expert system during times when the real instrument is not available.

5.1 Representation of Instrument Construction Knowledge

The knowledge about the physical construction of the TQMS is represented by an inheritance hierarchy of frames (Figure 9). Slots within the frames are used to handle the part/assembly knowledge and to relate the parts/assemblies with the controls (e.g. knobs and switches) that control them.

A second inheritance hierarchy encodes the knowledge of the instrument controls (Figure 10). A Slot within these frames relates the control to the part/assembly it controls. Slots within the "knobs" frames encode such knowledge as the knobs limits, its current setting, the DAC step size, etc. as this knowledge is fundamental to optimizing performance using the knob.

Separation of this knowledge into two inheritance hierarchies (parts and controls), with accompanying Methods for producing the TQMS part/whole graph, (Figure 11) improved the transparency of the representation, increased the usefulness of inheritance, and provides a clear depiction of the part/whole breakdown of the instrument.

The instrument representation also made possible the use of "virtual knobs" or "linked knobs". A "virtual knob" controls two or more knobs (and therefore one or more parts) simultaneously, giving them a single setting as though they are controlled by a single physical knob. TQMS experts had previously determined that the settings of certain physical knobs should be varied together, but were unable to effectively do this while manually tuning the instrument. The addition of virtual knobs permitted such simultaneous variation at only the cost of the programming necessary to implement the mapping from the setting of the virtual knob to the settings of the controlled knobs. A Method, or a Method plus a rule set, were used to represent the procedural knowledge of these mappings.

5.2 Representation of the Procedural Tuning Knowledge

As previously mentioned, a "Method" is used to encode the top-level iterative tune steps. In addition, this method also handles any bookkeeping necessary such as remembering which knobs have been tweaked and displaying the tune progress. Use of a "Method" for this knowledge representation task has been reasonable as LISP code is well suited to the procedural, sequential nature of the task.

However, because "methods" are not well suited to representing knowledge about making complex, heuristic decisions, Rules were used to select the knob to tweak at each iteration. In addition, additional rule bases were used to make the subsequent decisions concerning the optimization algorithm to be used, the type of instrument performance to be optimized, etc.

5.3 Representation of the Output Evaluation Procedures

Knowledge of how to evaluate the signal obtained from the instrument is required during the tuning process. In the knob selection step, the peak waveform needs to be analyzed to determine if any problems with peak shape or width exist. This knowledge is then combined with knowledge about the current state of the tuning process and knowledge about which knobs have recently been tweaked to select the knob which will most likely produce the greatest increase in instrument performance. Thus the evaluation process is necessary at the beginning of each iteration in the tuning process as it provides the necessary feedback to direct the expert system quickly towards the final optimized state.

Rules are used to evaluate a condensed description of the peak waveform and work in concert with the rules that select the knob to tweak. Rules were chosen for the output evaluation process because they provide a flexible mechanism for evaluating the different factors in the peak waveform at a time when complete evaluation is critical to system performance. The evaluation rules are placed in the same rule set as the rules that select the knob to tweak, allowing them to be tailored to their companion knob selection rules.

The second point at which it is necessary to evaluate the instrument output is during the tweaking step. Constant evaluation of the instrument output is necessary to adjust the knob so that optimum performance is achieved. However, total evaluation of the peak waveform is not necessary since only a single measure of overall performance can be used by the existing tweaking procedures. Accordingly, a Method is used to encode the knowledge necessary to convert the condensed peak description into a single numeric performance measure.

5.4 Representation of Interfacing Knowledge

The knowledge of how to interface the TOMS expert system to the LSI-11 control computer is partitioned into two pieces. The first part interfaces the functionality of the instrument to the instrument representation scheme. This part is represented using Frames and Methods; the hierarchy of these frames is shown in Figure 12. The Frames and Methods represent the knowledge necessary to command the LSI-11 computer to manipulate any of the TQMS controls and to solicit any acquired/processed data from the LSI-11 computer.

The second part of the interfacing knowledge encodes the procedures for communicating between the Xerox 1109, used for the AI programming, and the LSI-11 computers used with the TQMS. It consists of LISP code that implements a low-level master/slave protocol to provide an interlocked, reliable communication path. LISP code was chosen because of the need for efficiency dictated by the Xerox 1109's RS-232C interface. The implementation uses hierarchal control and state machine emulation to reliably transfer commands and responses between the Xerox 1109 and the LSI-11 control computers. The RS-232C communication link was chosen because the interface was available on both machines and high bandwidth was not required.

6. RESULTS

The use of knowledge based systems techniques to automate the tuning of the TQMS has proven to be very useful. Initial results have demonstrated that the system is able to tune the instrument in MS mode nearly as well as a Simplex optimization procedure in one-half the time. Further, it tunes better than an expert operator does, but it takes twice as long (Figure 13). If the human expert optimizes on a single peak, then this human manual tuning takes less time than the expert system and it can attain twice the sensitivity. However, experts do not individually tune every peak in a mass region because it takes far too long; so a more valid comparison of the system performance is shown in Figure 14. Using the calibration compound perfluorotributylamine, and optimizing the instrument in four separate mass regions (less than 100, 100-200, 200-350, greater than 350) we are able to increase the peak intensity (and instrument sensitivity) in all regions by factors of 2 to 30. As more rules are added to the system and the current rules are optimized, the sensitivity should increase most noticeably in the region above mass 500 (6,7,8). Having demonstrated the usefulness of knowledge based systems to MS tuning, we turned to the more general and difficult optimization problem, that of MS/MS tuning.

MS/MS operation of the TQMS differs from single MS mode in that selected parent ions are further fragmented and mass analyzed before being detected. This collision process introduces new parameters and conditions which don't exist in single MS operations. For example, the energy of the collision in the second quadrupole is a new parameter to optimize.

In previous work (4), we showed the importance of linking key parameters of the TQMS together to achieve optimum tuning. Figure 15 illustrates that by showing the increased peak intensity achieved in linking only two variables, the Q3 field axis (FA3) with the Q2 field axis (FA2) at a fixed voltage offset. This increase in daughter ion sensitivity was very useful for MS/MS tuning. Now we have shown that by using a rule based system to determine which parameters should be linked, and by optimizing various key ratios between certain parameters (FA2 to FA3, interquad lenses to each other, Einzel lenses to FA2, etc.) we can achieve an even greater increase in sensitivity. Figure 16 is a plot of intensity (of the daughter ion at mass 219 from the parent ion at mass 502 from perfluorotributylamine, PFTBA) vs. the collision energy. The lower intensity curve shows a typical energy profile which can be obtained by manual optimization of the FA2 instrument parameter. The rule-based virtual knob which we have developed links several of the parameters together and produces a dramatic increase in sensitivity (a factor of 40). This increased sensitivity was never obtained by manual tuning methods or by our previous linked methods, but is easily accomplished with the AI automated optimization scheme.

7. CONCLUSION

The interfacing of the expert system to the TQMS proved the value of expertise, encoded in the form of rules, to complex optimization problems. The system is able to optimize the output of a complex instrument running chemical compounds in a way not practical with manual methods. Because the expert system approach allows the instrument to be tuned quickly, multiple mass range, or even individual mass pair tuning is now practical, resulting in large gains in instrument sensitivity.

Two significant problems with the application of knowledge based systems to chemical instrumentation have been encountered. First, there is a significant learning curve associated with applying the technology, and second, the knowledge based systems software tools and the supporting hardware are expensive. While our experience has shown that the hardware and software tools are cost effective for developing the system, these high costs make fielding multiple copies of the expert system, using the total development environment like KEE provides, economically prohibitive. The alternative is to port the development system to other hardware using conventional languages, but this approach is practical only where the large costs of porting the software can be amortized over many systems.

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DISCLAIMER

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FIGURE CAPTIONS

Figure 1. Structural features and operational modes of a triple quadrupole mass spectrometer (TQMS)

Figure 2. Multidimensional nature of TQMS mass spectrometric data showing sulfur compounds

Figure 3. Example of "good tuning" vs. "bad tuning" of a peak

Figure 4. First attempts: Manual Tuning vs. Expert System Tuning (peak intensity maximized, no peak shape or resolution factors included)

Figure 5. Second attempts: Manual Tuning vs. Expert System tuning ("Goodness" function to incorporate peak shape and resolution included)

Figure 6. Rule structure for field axis tuning

Figure 7. TQMS icon with "Chez TQMS menu" and tuning plots shown

Figure 8. Tuning points for optimization of Q1 Field axis

Figure 9. Relationship between part or assembly knowledge and controls or knob. Bold face type = Knobs, which exert control over the, normal face type = parts

Figure 10. Inheritance hierarchy encoding knowledge of instrument controls

Figure 11. Part/whole breakdown of the instrument

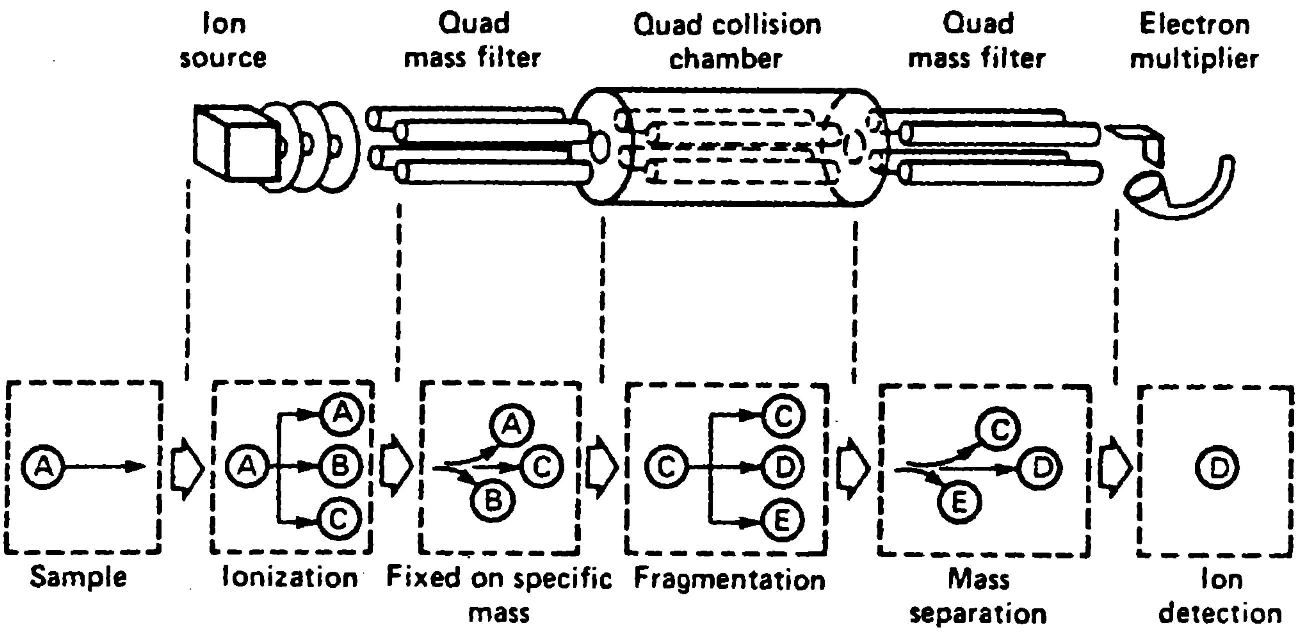
Figure 12. Interface or hooks between TQMS expert system and the instrument

Figure 13. Comparison of expert system, manual and Simplex methods of optimization

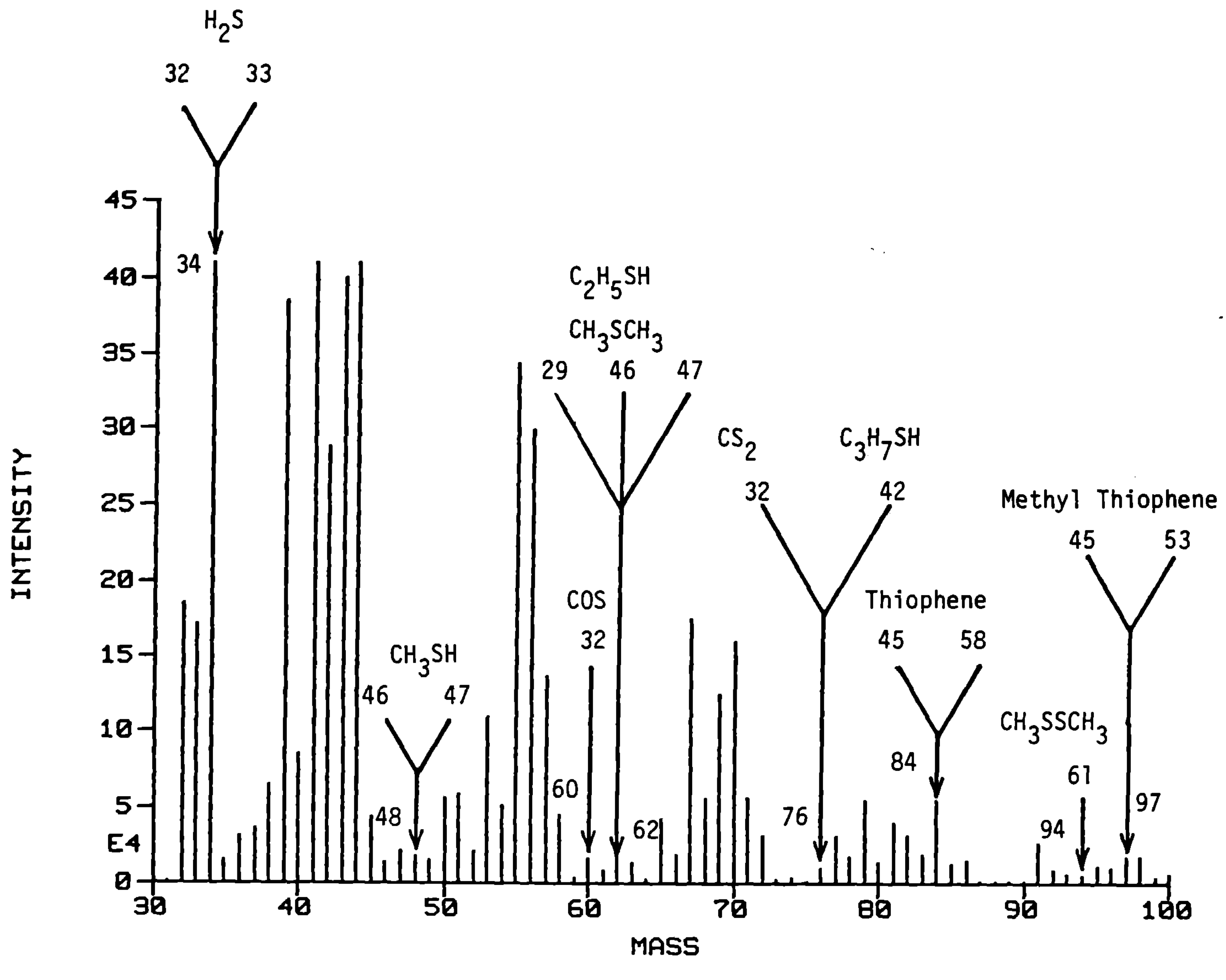
Figure 14. Comparison between normal manual tuning and optimized tuning on PFTBA

Figure 15. Comparison of linked vs. unlinked tuning of field axis in MS/MS parent-daughter mode

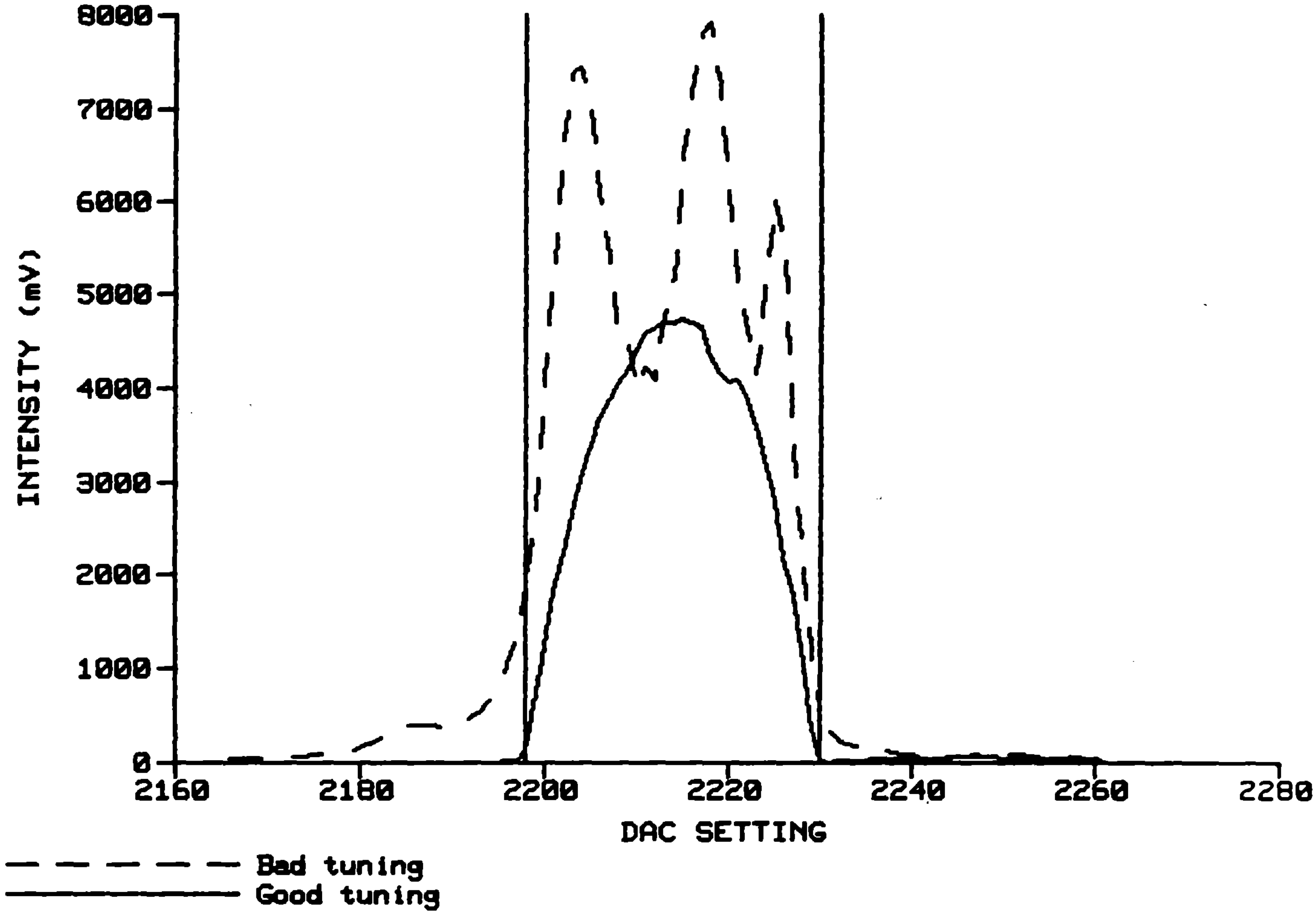
Figure 16. Comparison of manual vs. "virtual knob" multiple parameter linked tuning



Operation Mode	Quad 1	Quad 2	Quad 3	Results
1	Separated by mass	All masses passed No gas	All masses passed	Normal mass spectrum
2	Fixed on specific mass	All masses passed Collision gas	Separated by mass	Spectrum of all daughter ions from the selected parent ion
3	Separated by mass	All masses passed Collision gas	Fixed on specific mass	Spectrum of parent ions that fragment to give specific daughter ion
4	Separated by mass	All masses passed Collision gas	Separated by mass	Fixed mass difference between 2 scanning quads gives specific neutral mass loss
5	Fixed on specific mass	All masses passed Collision gas	Fixed on specific mass	Single or multiple reaction monitoring



H2S
32
33
34
C2H5SH
CH3SCH3
29
46
47
CS2
C3H7SH
32
42
Methyl Thiophene
45
53
Thiophene
45
58
COS
32
CH3SH
46
47
48
60
62
76
84
CH3SSCH3
61
94
97
INTENSITY
45
40
35
30
25
20
15
10
5
E4
0
30
40
50
60
70
80
90
100
MASS


8000
7000
6000
5000
4000
3000
2000
1000
0
INTENSITY (mV)
2160
2180
2200
2220
2240
2260
2280
DAC SETTING
Bad tuning
Good tuning

MASS RANGE 31-131

SEM = 1100 V, AUTORANGING 10^{-7}

SCANNING Q3

MANUAL TUNING

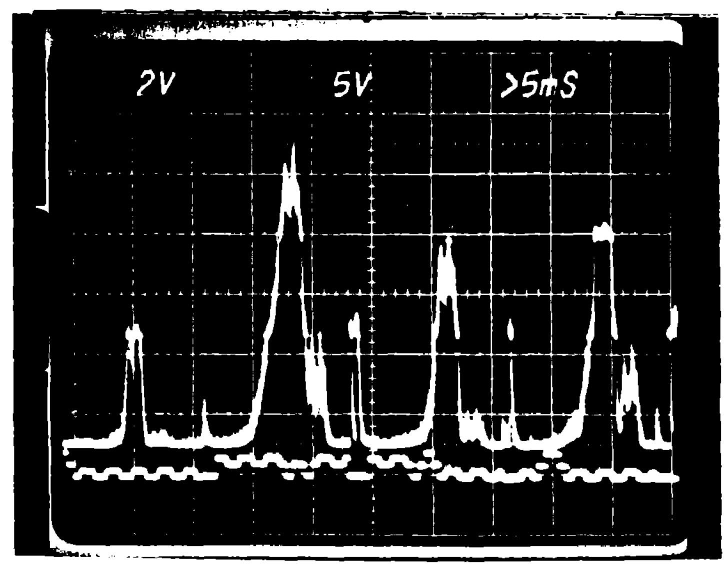
AMU: 31 69 100 131

MASS RANGE 31-131

SEM = 1100 V, AUTORANGING 10^{-7}

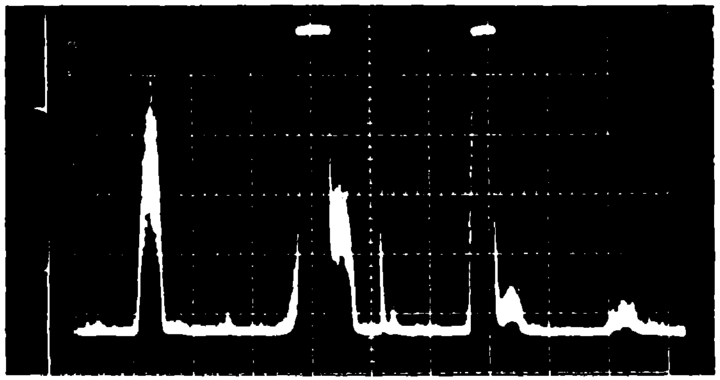
SCANNING Q3

DOLPHIN AI TUNING

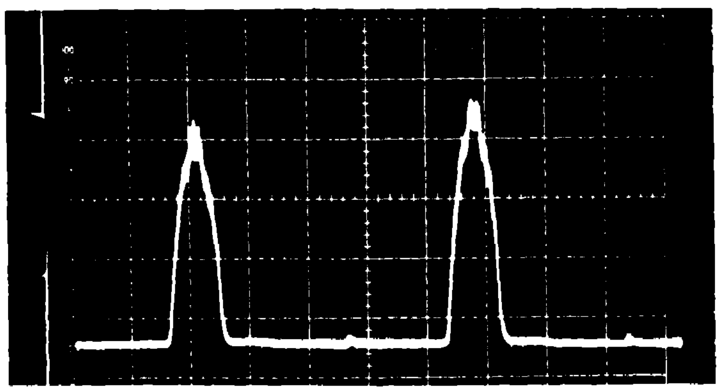


AMU: 31 69 100 131

NORMALIZED MANUAL TUNING

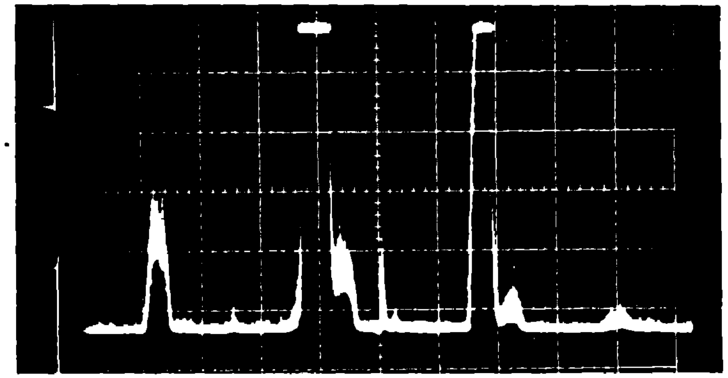


31 69 219 502

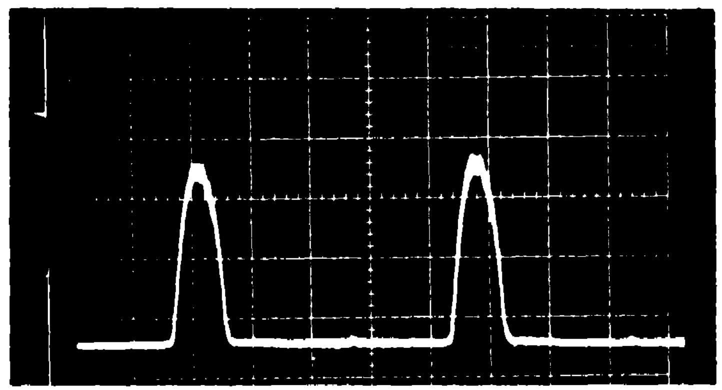


69

AI TUNING



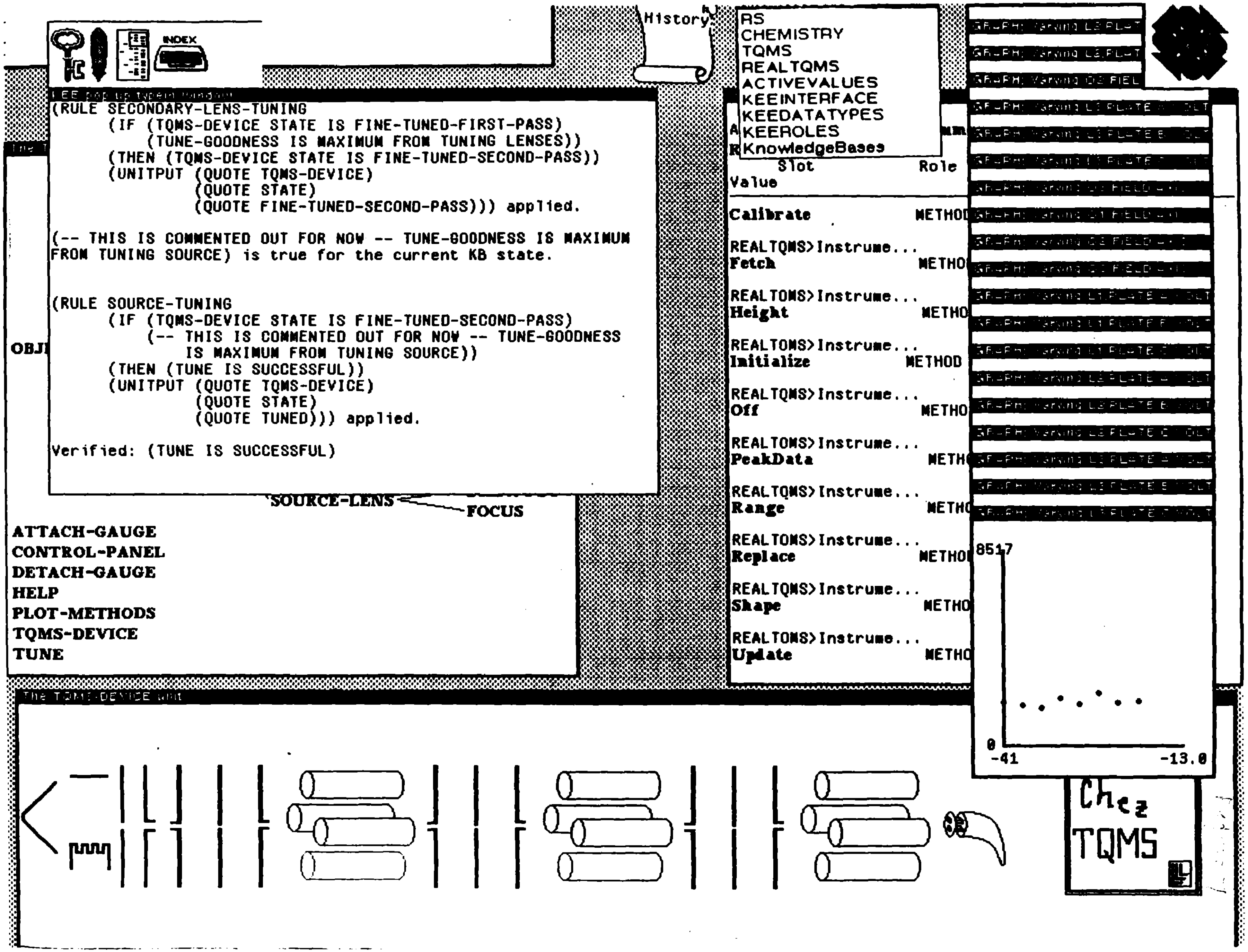
31 69 219 502



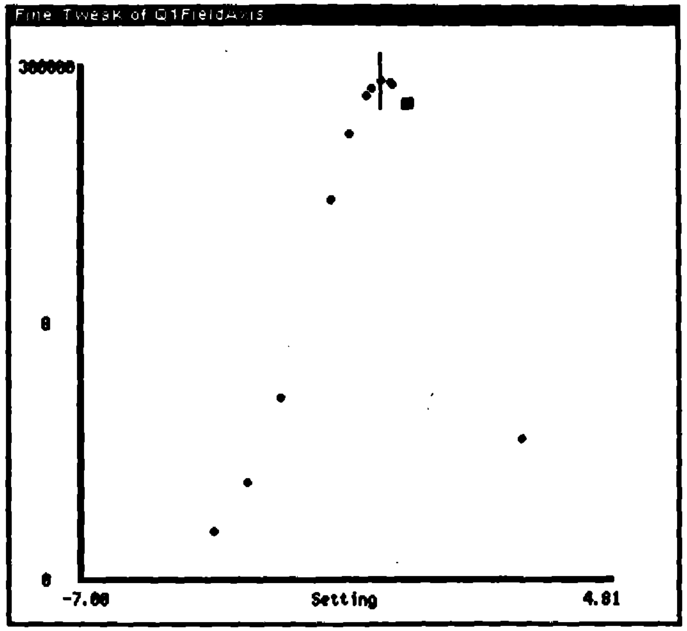
69

(OUTPUT) The RULES slot

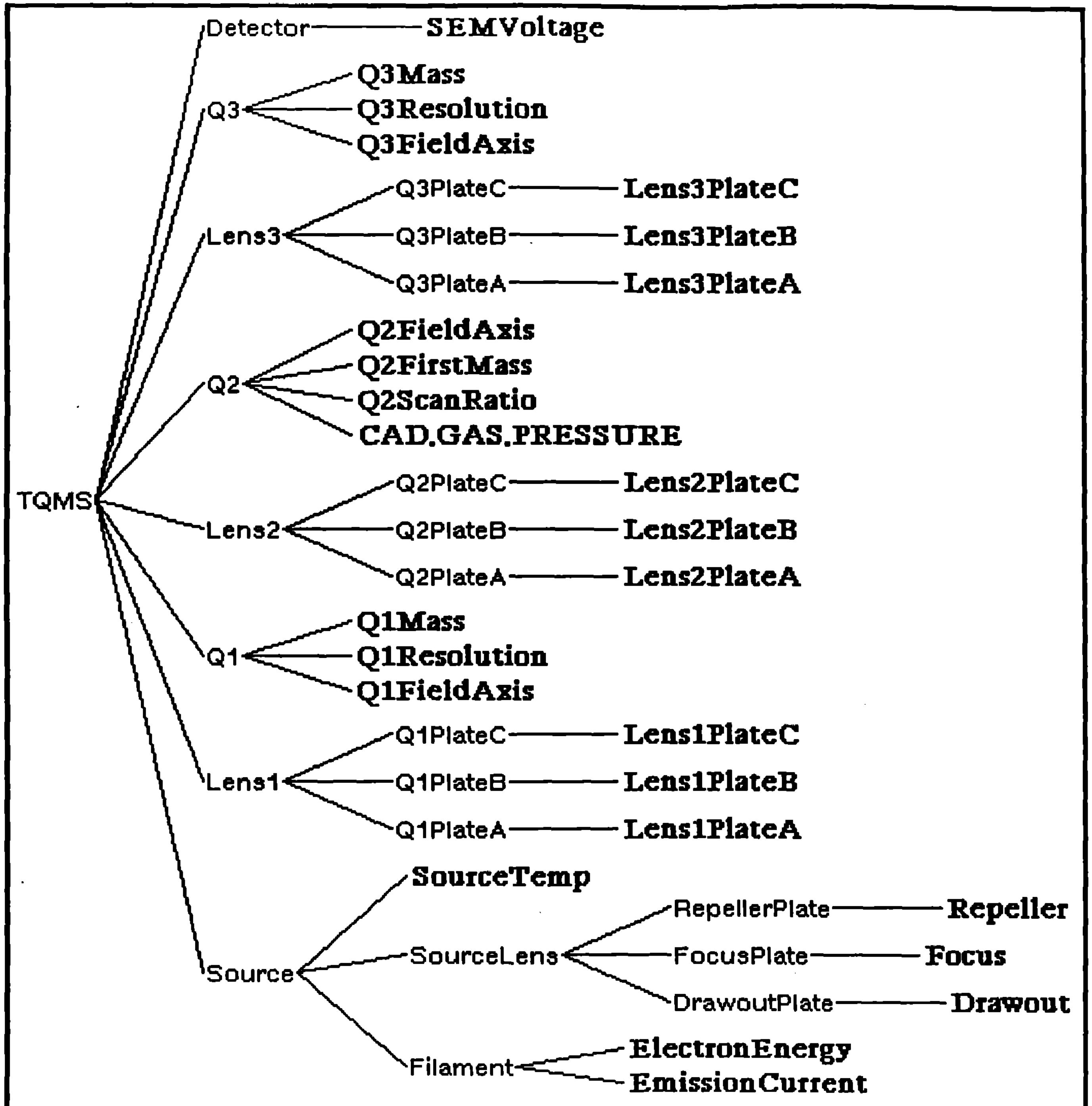
```
OwnSlot: RULES from NOTHING
   Inheritance: OVERRIDE.VALUES
   ValueClass: LIST
   Values: (RULE FA-TUNING
                  (IF (TUNE GOODNESS IS MAXIMIZED BY VARYING Q1 FIELD.AXIS)
                      (TUNE GOODNESS IS MAXIMIZED BY VARYING Q2 FIELD.AXIS)
                      (TUNE GOODNESS IS MAXIMIZED BY VARYING Q3 FIELD.AXIS))
                  (THEN (TUNE-GOODNESS IS MAXIMIZED FROM TUNING FIELD-AXIS)))
            [RULE INITIAL-TUNING
                  (IF (TQMS-DEVICE STATE IS UNTUNED)
                      (TUNE-GOODNESS IS MAXIMIZED FROM TUNING LENSES AND
                                     FIELD-AXIS))
                  (THEN TQMS-DEVICE STATE IS COARSE-TUNED)
                  (PROGN (UNITPUT (QUOTE TUNE)
                                  (QUOTE MODE)
                                  (QUOTE FINE))
                         (UNITPUT (QUOTE TQMS-DEVICE)
                                  (QUOTE STATE)
                                  (QUOTE COARSE-TUNED]
            (RULE INITIAL-FIELD-AXIS-TUNING
                  (IF (TQMS-DEVICE STATE IS COARSE-TUNED)
                      (TUNE-GOODNESS IS MAXIMIZED FROM TUNING FIELD-AXIS)))
```



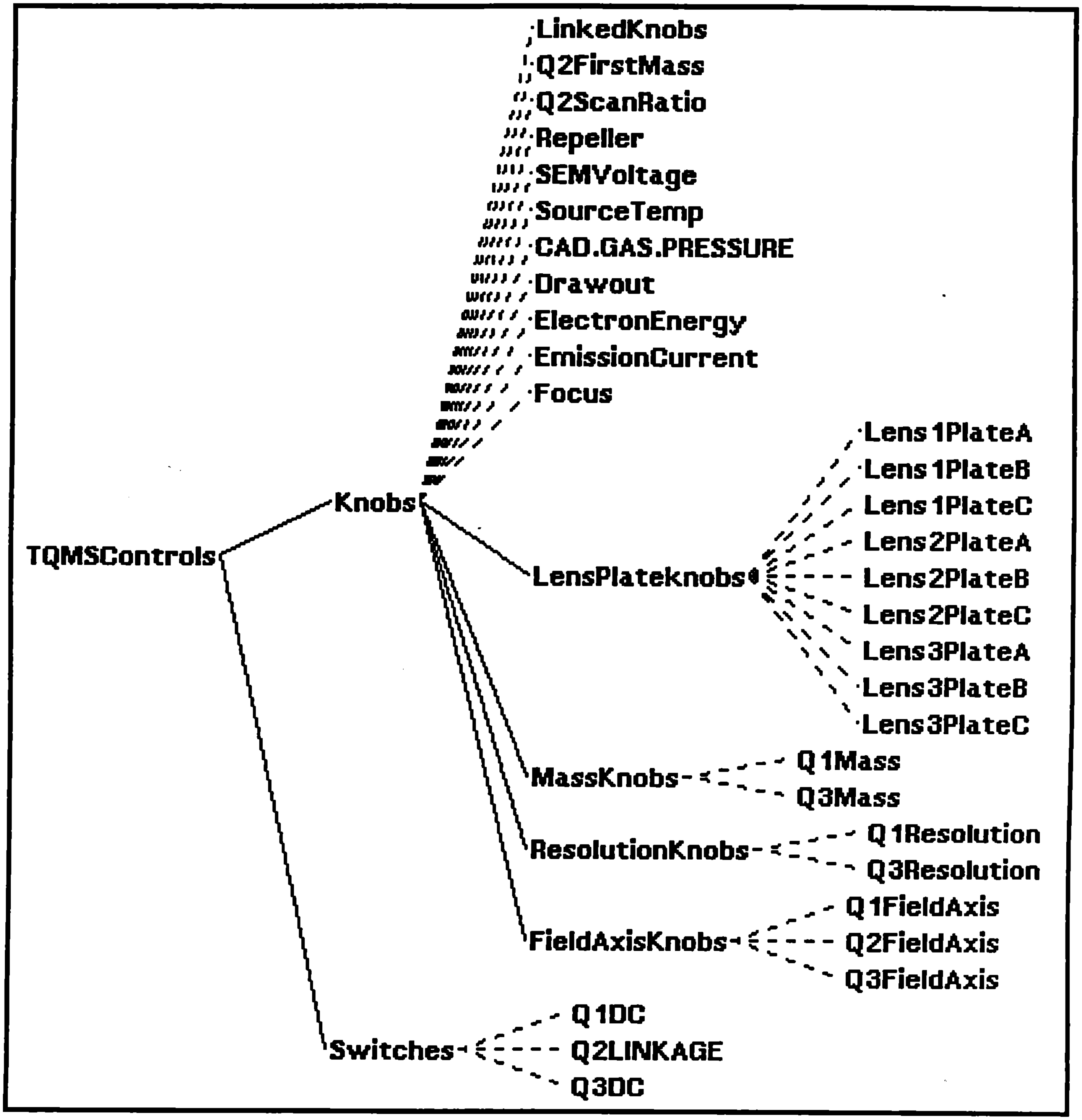
History
RS
CHEMISTRY
TQMS
REALTQMS
ACTIVEVALUES
KEEINTERFACE
KEEDATATYPES
KEEROLES
KnowledgeBases
INDEX
(RULE SECONDARY-LENS-TUNING
(IF (TQMS-DEVICE STATE IS FINE-TUNED-FIRST-PASS)
(TUNE-GOODNESS IS MAXIMUM FROM TUNING LENSES))
(THEN (TQMS-DEVICE STATE IS FINE-TUNED-SECOND-PASS))
(UNITPUT (QUOTE TQMS-DEVICE)
(QUOTE STATE)
(QUOTE FINE-TUNED-SECOND-PASS))) applied.
(-- THIS IS COMMENTED OUT FOR NOW -- TUNE-GOODNESS IS MAXIMUM FROM TUNING SOURCE) is true for the current KB state.
(RULE SOURCE-TUNING
(IF (TQMS-DEVICE STATE IS FINE-TUNED-SECOND-PASS)
(-- THIS IS COMMENTED OUT FOR NOW -- TUNE-GOODNESS IS MAXIMUM FROM TUNING SOURCE))
(THEN (TUNE IS SUCCESSFUL))
(UNITPUT (QUOTE TQMS-DEVICE)
(QUOTE STATE)
(QUOTE TUNED))) applied.
Verified: (TUNE IS SUCCESSFUL)
Slot
Role
Value
Calibrate METHOD
REALTQMS>Instrume...
Fetch METHO
REALTQMS>Instrume...
Height METHO
REALTQMS>Instrume...
Initialize METHOD
REALTQMS>Instrume...
Off METHO
REALTQMS>Instrume...
PeakData METH
REALTQMS>Instrume...
Range METHO
REALTQMS>Instrume...
Replace METHO
REALTQMS>Instrume...
Shape METHO
REALTQMS>Instrume...
Update METHO
OBJ
SOURCE-LENS
FOCUS
ATTACH-GAUGE
CONTROL-PANEL
DETACH-GAUGE
HELP
PLOT-METHODS
TQMS-DEVICE
TUNE
8517
0
-41
-13.0
The TQMS-DEVICE unit
Chez TQMS

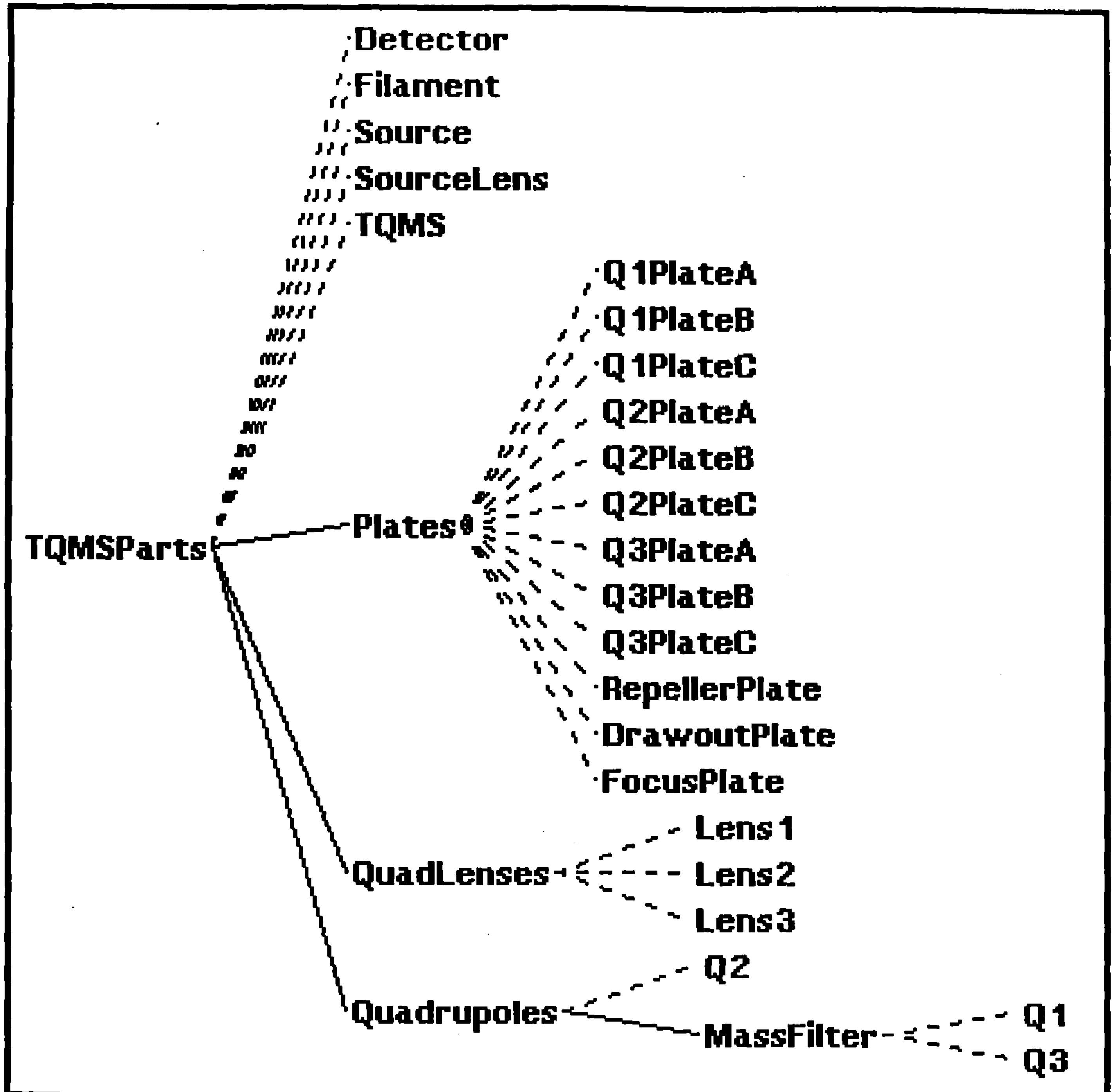


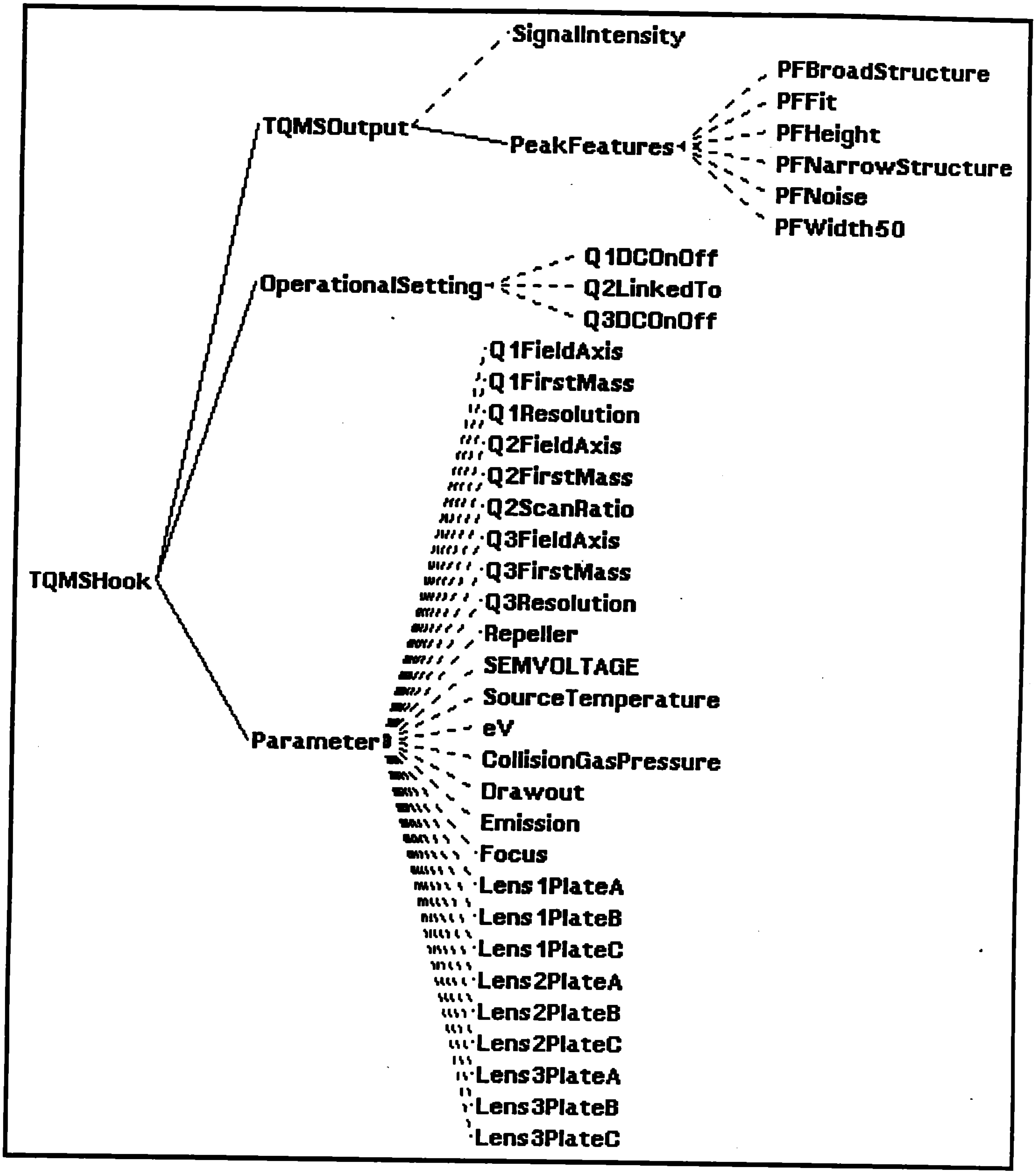
Fine Tweak of Q1FieldAxis
300000
0
0
-7.00
Setting
4.81

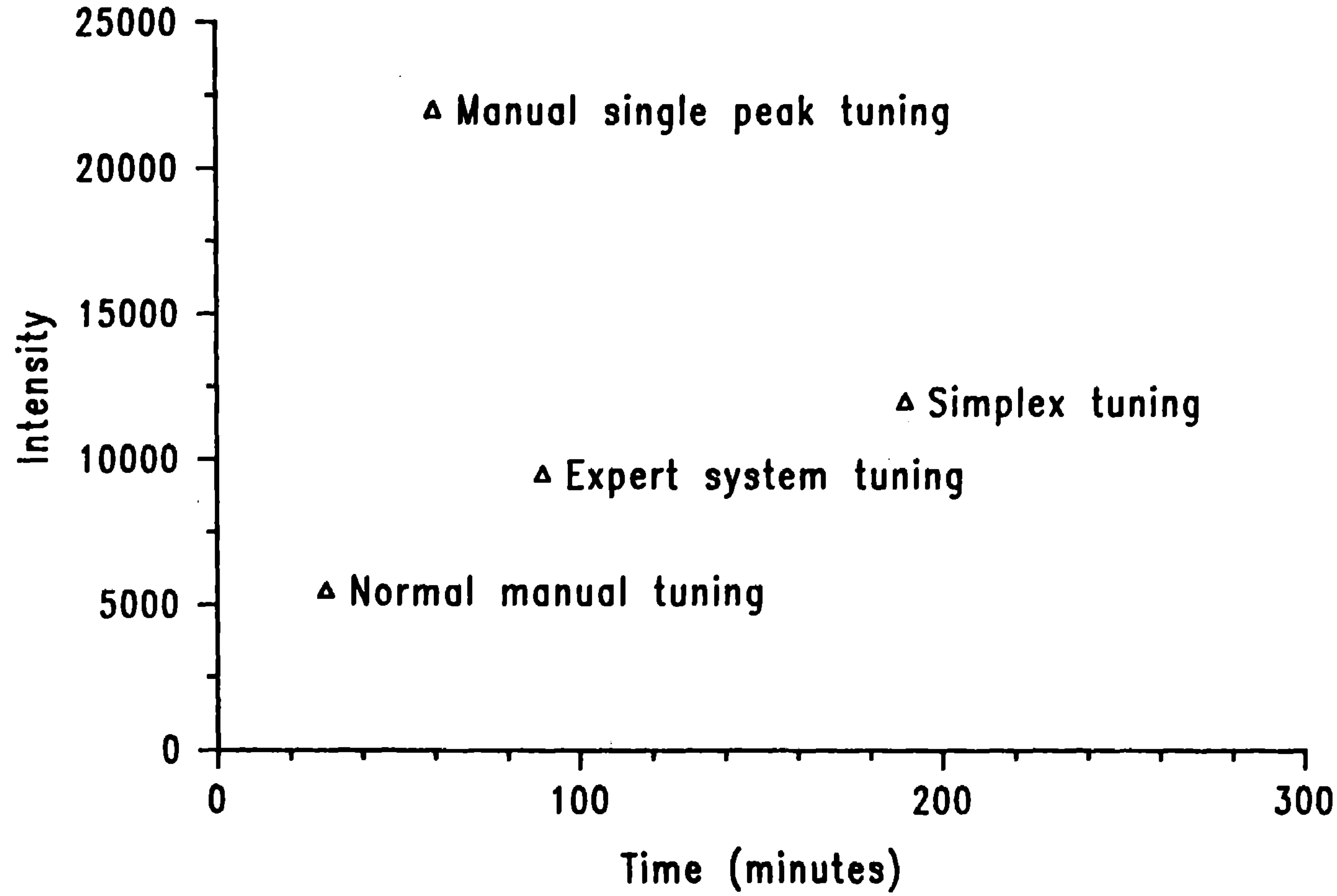


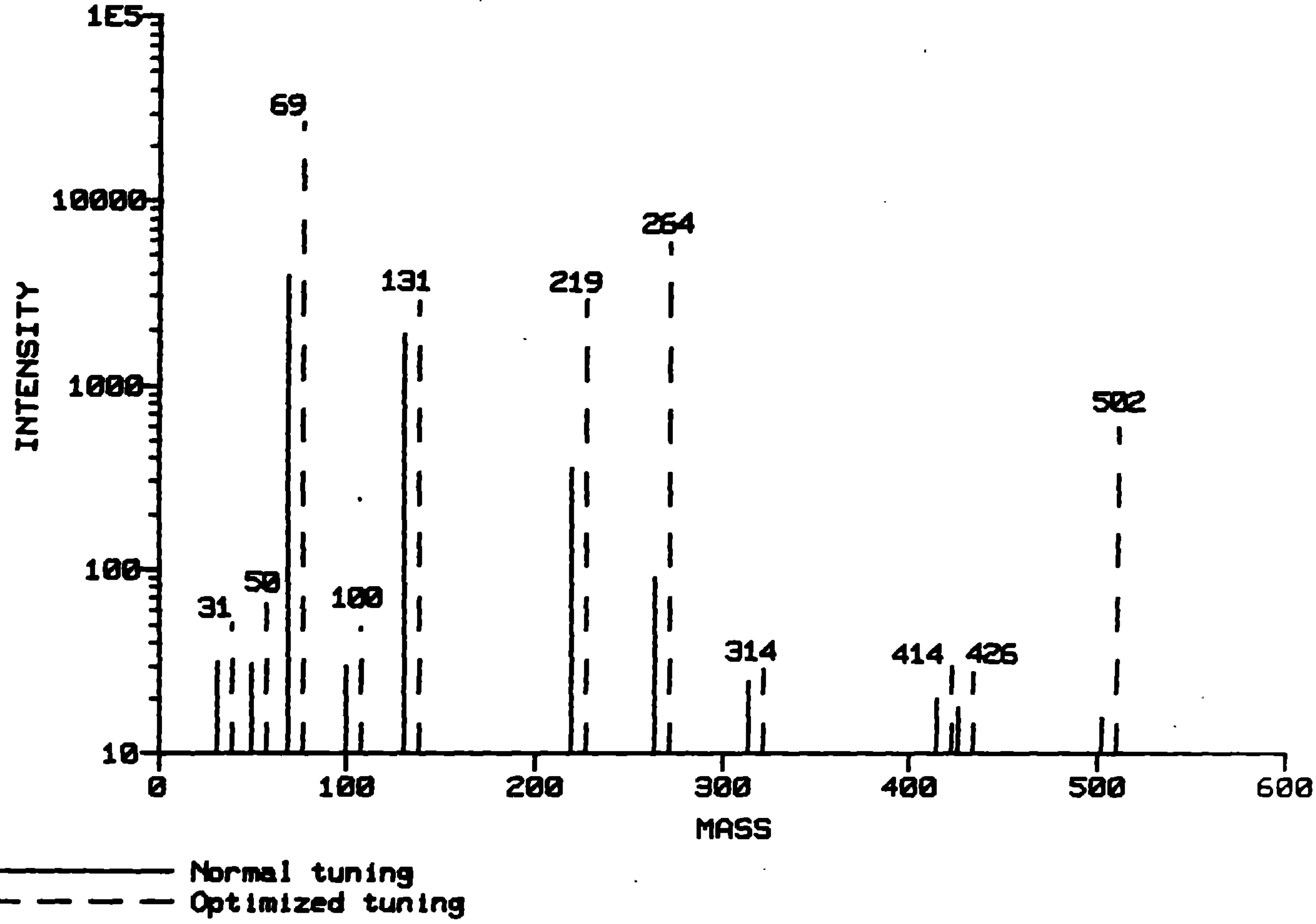
TQMS
Detector
SEMVoltage
Q3
Q3Mass
Q3Resolution
Q3FieldAxis
Lens3
Q3PlateC
Lens3PlateC
Q3PlateB
Lens3PlateB
Q3PlateA
Lens3PlateA
Q2
Q2FieldAxis
Q2FirstMass
Q2ScanRatio
CAD.GAS.PRESSURE
Lens2
Q2PlateC
Lens2PlateC
Q2PlateB
Lens2PlateB
Q2PlateA
Lens2PlateA
Q1
Q1Mass
Q1Resolution
Q1FieldAxis
Lens1
Q1PlateC
Lens1PlateC
Q1PlateB
Lens1PlateB
Q1PlateA
Lens1PlateA
Source
SourceTemp
SourceLens
RepellerPlate
Repeller
FocusPlate
Focus
DrawoutPlate
Drawout
Filament
ElectronEnergy
EmissionCurrent


TQMSControls
Knobs
LinkedKnobs
Q2FirstMass
Q2ScanRatio
Repeller
SEMVoltage
SourceTemp
CAD.GAS.PRESSURE
Drawout
ElectronEnergy
EmissionCurrent
Focus
LensPlateknobs
Lens1PlateA
Lens1PlateB
Lens1PlateC
Lens2PlateA
Lens2PlateB
Lens2PlateC
Lens3PlateA
Lens3PlateB
Lens3PlateC
MassKnobs
Q1Mass
Q3Mass
ResolutionKnobs
Q1Resolution
Q3Resolution
FieldAxisKnobs
Q1FieldAxis
Q2FieldAxis
Q3FieldAxis
Switches
Q1DC
Q2LINKAGE
Q3DC

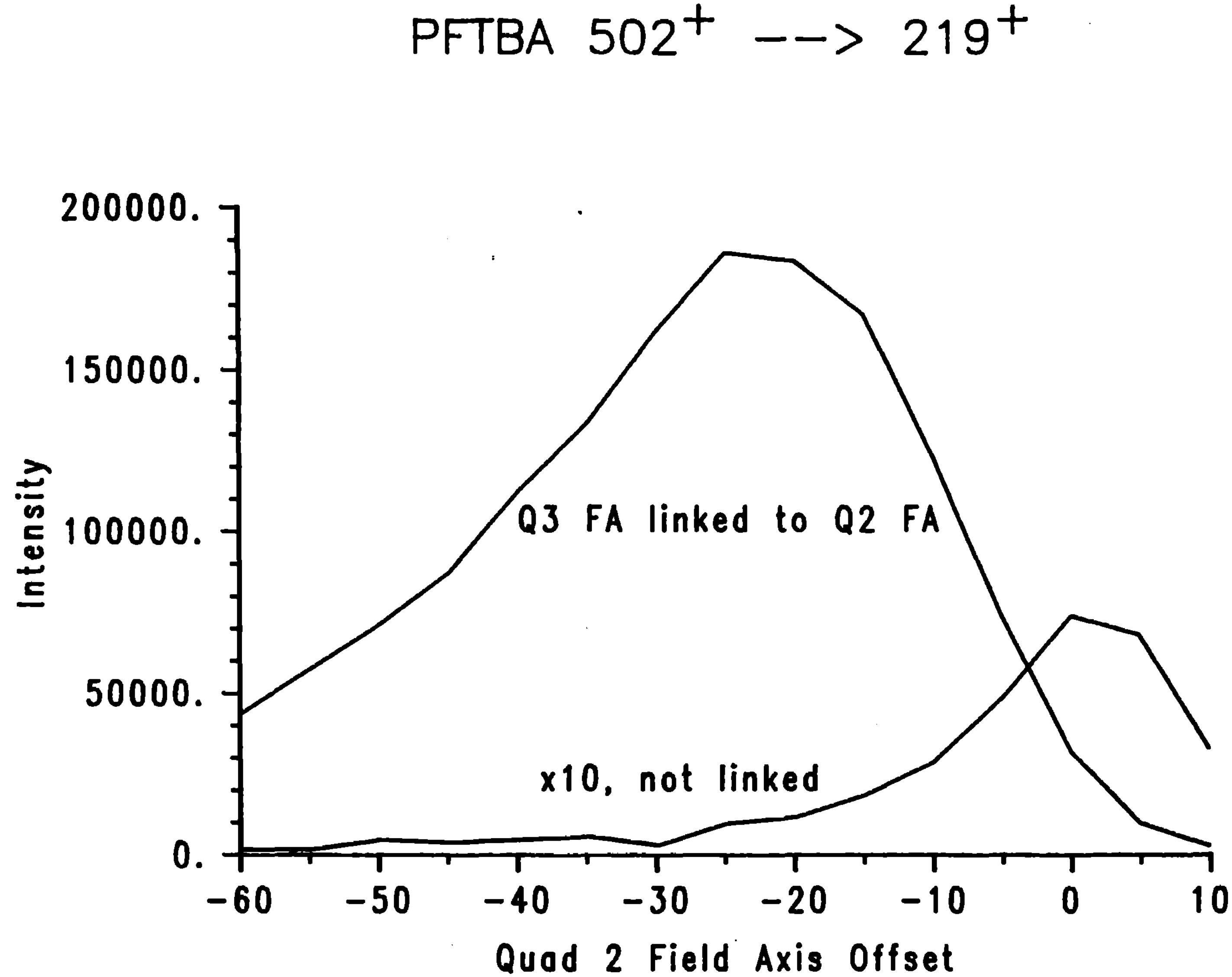

TQMSParts
Detector
Filament
Source
SourceLens
TQMS
Plates
Q1PlateA
Q1PlateB
Q1PlateC
Q2PlateA
Q2PlateB
Q2PlateC
Q3PlateA
Q3PlateB
Q3PlateC
RepellerPlate
DrawoutPlate
FocusPlate
QuadLenses
Lens1
Lens2
Lens3
Quadrupoles
Q2
MassFilter
Q1
Q3


TQMSHook
TQMSOutput
SignalIntensity
PeakFeatures
PFBroadStructure
PFFit
PFHeight
PFNarrowStructure
PFNoise
PFWidth50
OperationalSetting
Q1DCOnOff
Q2LinkedTo
Q3DCOnOff
Parameter
Q1FieldAxis
Q1FirstMass
Q1Resolution
Q2FieldAxis
Q2FirstMass
Q2ScanRatio
Q3FieldAxis
Q3FirstMass
Q3Resolution
Repeller
SEMVOLTAGE
SourceTemperature
eV
CollisionGasPressure
Drawout
Emission
Focus
Lens1PlateA
Lens1PlateB
Lens1PlateC
Lens2PlateA
Lens2PlateB
Lens2PlateC
Lens3PlateA
Lens3PlateB
Lens3PlateC


25000
20000
15000
10000
5000
0
Intensity
Manual single peak tuning
Simplex tuning
Expert system tuning
Normal manual tuning
0
100
200
300
Time (minutes)



1E5
10000
1000
100
10
INTENSITY
69
131
219
264
502
31
50
100
314
414
426
0
100
200
300
400
500
600
MASS
Normal tuning
Optimized tuning


PFTBA 502+ --> 219+
Intensity
200000.
150000.
100000.
50000.
0.
Q3 FA linked to Q2 FA
x10, not linked
-60
-50
-40
-30
-20
-10
0
10
Quad 2 Field Axis Offset

Snowbird Conference: June 1986 Carla Wong

Pattern Recognition methods in analytical Spectroscopy

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GUIDE FOR CONTRIBUTORS TO MODERN ANALYTICAL CHEMISTRY

These pages should be read very carefully by both the author and his typist. Meticulous attention to the instructions they contain will help not only the editor and the publisher, but also the author, since careful preparation of manuscript is the most important single factor assuring error-free printed text that precisely reflects the author's intent.

X1 -1c'
CN2-1
CN3-1
X4 -1
CN4-2
X5 -1
X5 -2
X6 -1c
X6 -2

1. General Instructions

a. An outline or summary should be submitted to your editor well in advance of delivery of the manuscript.

b. If any of the material to be included (illustrations, tables, quotations of more than a few words) is taken from another publication, you must obtain permission to use this material from the copyright owner and insert acknowledgments in the form he prescribes into your manuscript.

c. The ribbon copy of the manuscript, together with all the necessary artwork, photographs, figure captions, tables, references, etc., must be submitted to the editor on or before the date specified in the agreement.

1" margin

d. The manuscript must be typed double-spaced on one side of good-quality white or near-white paper, approximately 8-1/2x11 inches in size, with margins of at least one inch on all sides. (For detailed typing instructions, see Section 6.) Illustrations and tables must be prepared as specified in Sections 2 and 3. If your chapter contains unusual elements (illustrations, tables, or other material of unusual size, type, or conformation, unconventional symbols or arrangements, etc.), consult with your editor before such material is prepared in final form.

e. The first page of the manuscript should give the title of the chapter and the author's full name and affiliation. Do not use titles or degrees in the author's by-line, but do furnish the address to which proofs should be mailed.

f. The manuscript should be accompanied by a detailed table of contents.

g. Current American spelling should be used. Webster's Third New International Dictionary may be used as final authority for spelling and hyphenation. Recent issues of the leading journals in the field may serve as a guide to preferred technical terminology and symbolic notation.

h. Footnotes should be used only if it is not possible to incorporate the thought into the text without disrupting the flow of the argument. The placement of footnotes is indicated in the text by asterisks (or daggers, double-daggers, etc., if there is more than one footnote on a page). The footnotes themselves are to be collected and typed double-spaced on a separate sheet at the end of the text, each footnote being identified in the left margin by the number of the manuscript page to which it belongs.

2. Illustrations

a. All illustrations submitted must be suitable for reproduction without further retouching or redrawing. Original inked drawings yield the best results and should be submitted with the manuscript if available. If not, high-quality prints made from the original drawing are generally acceptable. Xerox copies are not acceptable, and photostats frequently give poor results.

b. Drawings should be prepared at approximately twice the desired final size, keeping in mind that the type area in the printed book will be approximately 4-1/2 x 7 inches, and that no illustration can exceed these final dimensions. The drawings should be fully lettered, and the lettering must be large enough to remain legible after reduction.

c. Drawings should be free of unnecessary detail. If possible, graphs should be prepared with ticks on the axes rather than grid lines. If grid lines must be shown, the drawings may be prepared on light blue, nonreproducing graph paper and the major grid lines inked in.

d. Photographs should be used only if absolutely necessary. Large glossy prints made from the original negative must be furnished. If less than the entire area of the photographic print need or should be shown in the book, indicate the area to be included on a tracing paper overlay.

e. If the magnification of a photograph has to be indicated, this should be done, whenever possible, by means of a scale superimposed on the photograph, rather than a numerical statement in the caption, since such a scale is not distorted by the reduction which the photograph may have to undergo to fit onto the page.

f. The illustrations in each chapter should be numbered in a single sequence of arabic numbers. Figures should be numbered in the order in which they are Figures mentioned in the text. All text references should employ the word "figure" rather than such varied designations as "diagram," "chart," "photograph," etc.

g. Each drawing or photograph ~~must be fully identified; the title of the book~~, the name of the author, and the figure number must be given, and (if necessary) an indication of which side is the top of the figure. This information should be written directly on the illustration or typed on strips of paper which are then glued (but not stapled or clipped) to the illustration. The information may be given in the margin of the illustration if it is sufficiently wide; otherwise it should appear on the back. In writing on the back of photographs, care must be taken not to make impressions that are visible on the face of the illustration.

h. Each figure must have a descriptive caption. The captions should be typed double-spaced in sequence on a separate sheet (or sheets) and should not be attached to the illustrations. Figures and captions should be placed at the end of the manuscript and should not be interspersed with the text.

5. References

a. Each author is responsible for the accuracy of his references. All names, dates, volume, and page numbers should be double-checked before the manuscript is submitted.

b. References should be numbered in the order of their first mention in the chapter. Text citations should take the form of raised numerals in parentheses. The citation may be used with or without the author's name: "...it has been shown by Johnson(17) that..." or "...experiments with calcium,(6) potassium,(7) and strontium(8) have shown...." Several references may be cited together, the numbers being separated by commas: "several recent investigations(6,7,9,15) indicate...." If three or more consecutive references are cited together, a dash should be used between the lowest and highest reference numbers: "...while others(10-14) show that...."

vB c. The reference list should be typed triple-spaced on a separate sheet or sheets, in the style indicated by the following examples:

1. C. E. Kuyatt and J. A. Simpson, Electron monochromator design, Rev. Sci. Instr. 38, 103-111 (1967).
2. R. W. Arnett, K. A. Warren, and L. O. Muller, Optimum Design of Liquid Oxygen Containers, Wright Air Development Center Technical Report 59-62 (August, 1961), p. 118.
3. R. Eisenschitz, Matrix Algebra for Physicists, Plenum Press, New York (1966).
4. J. A. Kaufman and E. W. Johnson, in: Advances in Cryogenic Engineering (K. D. Timmerhaus, ed.), Vol. 8, pp. 678-685, Plenum Press, New York (1963).

The examples illustrate the following characteristic cases:

1. A journal article. The article title is given, followed by the abbreviated name of the journal (in the form listed in Chemical Abstracts - List of Periodicals; names of journals or other periodical publications not listed there should be spelled out). The volume number is underlined and the first and last page numbers, rather than just the first, are given. For journals with unnumbered volumes, the year takes the place of the volume number: J. Chem. Soc. 1965, 2516-2522. For journals that start the pagination of each issue with 1, the issue number must be given in parentheses following the volume number: Pribory i Tekhn. Eksperim. 7(3), 53-57 (1962).

2. For pamphlets, bulletins, or any publications other than "regular" books or journals, give all the information available and do not use abbreviations.

3. A simple book reference.

4. A section in a multiauthor book.

d. Do not use "ibid.," "op.cit.," or "loc.cit." references, and do not use the abbreviation "et al." in the reference list, but list all authors, even when there are very many. However, the text reference in such a case may take the form "...shown by Jones et al.(7)...."

6. Typing Instructions

a. Paper: Use opaque white or near-white paper of good quality, approximately 8-1/2x11 inches in size. Do not use tissue or other lightweight papers, nor easy-erasing papers on which it is difficult to write.

b. Typewriter: Use an elite or pica typewriter in good condition. Make sure the keys are clean and the ribbon is not excessively worn. Do not use a typewriter with a face smaller than elite or larger than pica, nor one with a script typeface or a typeface in which the lower-case letters are merely smaller versions of the capital letters.

c. Margins: Leave one-inch margins on all four sides of the page.

d. Spacing: All the material without exception is to be at least double-spaced. The 1-1/2 spacing that some machines can provide is not sufficient. If it is necessary to set off material in the text (e.g., quotations or lists), this should be done by indentation, i.e., changing the margins, and not by single-spacing.

e. Paragraphing: Indent the first line of each paragraph five spaces. The "blocked" style that looks so good in letters can lead to confusion in a manuscript.

f. Headings: Number the major subdivisions of the chapter consecutively, using arabic numerals. Type subheadings of the same value in the same manner throughout the manuscript. The following style is suggested:

1. FIRST-VALUE SUBHEADING

1.1. Second-Value Subheading

1.1.1. Third-Value Subheading

1.1.1a. Fourth-Value Subheading. The first three values are typed on separate lines; the fourth is typed as the beginning of a paragraph. Except for first-value headings, all digits except the last are exactly those of the preceding subheading of next higher rank.

g. Numbering: Arrange the material in the following sequence, and number the sheets consecutively:

Title page
Table of contents
Text
Footnotes
References
Tables
Figure Captions

Note that each item in this list is to start on a new page and that, moreover, each chapter and each individual table is to start on a new page. Remember that the references are to be triple-spaced, all other material double-spaced, and that no part of any of these items is to be single-spaced.

h. Punctuation: Observe the following typing rules with respect to punctuation marks.

1. The comma and period are always typed before rather than after the closing quotation marks. Other punctuation marks are typed before the closing quotation marks if they are part of the quoted material and after the quotation marks if they are not.

2. If parentheses enclose one or more complete sentences, a period is used just inside the closing parenthesis. If parentheses at the end of a sentence enclose less than a full sentence, the period follows the closing parenthesis.

3. Superscript numerals (for literature references) and asterisks (for footnotes) should be typed after a comma or period but before any other punctuation mark.

4. Numbers, Units, Symbols, and Equations

a. Numbers up to ten should generally be spelled out, but numerals should be used for numbers from 11 up, except that numerals are always used in conjunction with symbols and units of measurement. Commas should separate groups of three digits in numbers of five or more digits (12,583) but no commas should be used in numbers of four digits (5837) unless they are aligned in a column with numbers that do contain commas:

```
1,356,789
   78,652
    5,382
```

Numbers between zero and one should be written with a cipher in front of the decimal point (0.5 — never .5).

b. The International System (SI) of units should be used. Units should be abbreviated when used with numerals but written out when they occur in the text without numerals. The abbreviations listed below should be employed. Note that these abbreviations are used without periods:

ampere	A	lux	lx
calorie	cal	meter	m
candela	cd	mho	spell out
coulomb	C	micrometer	μm
cubic meter	m^3	microliter	μl
curie	Ci	milligram	mg
decibel	db	milliliter	ml
degree Centigrade	°C	millimeter	mm
degree Kelvin	°K	millimeter of mercury	mm Hg
degree (angle)	°	million electron volts	MeV
dyne	dyn	millivolt	mV
electron volt	eV	mole	mol
erg	spell out	nanometer	nm
farad	F	newton	N
gauss	G	ohm	Ω
gram	g	ohm-centimeter	Ω-cm
henry	H	parts per million	ppm
hertz	Hz	percent	%
hour	h	radian	rad
joule	J	roentgen	R
kiloelectron volt	keV	second (time)	s
kilogram	kg	second (angle)	"
kilometer	km	square meter	m^2
kilovolt	kV	steradian	sr
kilowatt	kW	tesla	T
lambert	L	torr	Torr
liter	spell out	volt	V
lumen	lm	watt	W
		weber	Wb

c. The unit abbreviations listed above stand for the plural as well as the singular. Write 5 cm, not 5 cms.

d. The following prefixes may be combined with the basic unit abbreviations:

d	deci	(10^{-1})	da	deka	(10)
c	centi	(10^{-2})	h	hecto	(10^{2})
m	milli	(10^{-3})	k	kilo	(10^{3})
μ	micro	(10^{-6})	M	mega	(10^{6})
n	nano	(10^{-9})	G	giga	(10^{9})
p	pico	(10^{-12})	T	tera	(10^{12})

e. Mathematical and symbolic material in display equations and in the body of the text must be typed or written with great care. Handwritten greek letters and other special symbols must be identified by name at their <u>first</u> occurrence. Bold letters must be identified by a wavy underline at <u>each</u> occurrence. If it is necessary to use symbols from fonts other than the usual italic or bold (script, German, etc.), this may be indicated by color-coded underscores.

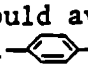
f. Particular care must be taken to differentiate clearly between the letter l and the numeral 1, the italic letter k and the greek kappa, the italic w and the greek omega, and also between the capital and lower-case forms of such letters as c, k, o, p, s, u, v, w, x, and z.

g. Built-up fractions and other notation requiring more than one line of type (this does not include subscripts and superscripts) should be avoided in the text proper, and if it must be used at all should be displayed. Simple fractions can be converted to one-line form, using the solidus:

$$\frac{a + b}{c} = (a + b)/c \qquad \cos\frac{x}{2} = \cos\,(x/2)$$

Parentheses must be used when ambiguities would otherwise result.

h. Display equations should be numbered with arabic numbers in parentheses in the right margin. Text references to the equations should echo this notation.

i. The chemical notation selected should avoid ring structures and vertical side chains whenever possible. Cl——OH may without loss of clarity be written as p-ClC_6H_4OH or

$$\begin{array}{c} CH_3 \\ | \\ CH_3\text{-}CH_2\text{-}C\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_3 \\ | \\ CH_3 \end{array} \quad \text{as} \quad CH_3CH_2C(CH_3)_2(CH_2)_3CH_3$$

e. Please distinguish between straightforward citation of literature references, which is the subject of this section, and comments or explanations that involve literature citations, which should be treated as footnotes (see Section 1h). For example, the sentence "A formal proof of this theorem is given in Eisenschitz, Matrix Algebra for Physicists, Plenum Press, New York (1966)" has no place in a list of references. Instead, it should take the form of a footnote: "A formal proof of this theorem is given by Eisenschitz[3]" with the formal citation being given as (3) in the list of references.